Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Clinical practice guideline on the management of lipids as a cardiovascular risk factor.

Bibliographic Source(s)

San Vicente Blanco R, PÃ©rez Irazusta I, Ibarra Amarica J, Berraondo Zabalegui I, Uribe Oyarbide F, Urraca GarcÃa de Madinabeitia J, Samper Otxotorena R, Aizpurua Imaz I, Almagro Mugica F, AndrÃ©s Novales J, Ugarte Libano R. Clinical practice guideline on the management of lipids as a cardiovascular risk factor. Vitoria-Gasteiz: Basque Health System-Osakidetza; 2008. 215 p.

Guideline Status

This is the current release of the guideline.

The Basque Health System-Osakidetza reaffirmed the currency of this guideline in June 2013.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- April 8, 2016 – Metformin-containing Drugs : The U.S. Food and Drug Administration (FDA) is requiring labeling changes regarding the recommendations for metformin-containing medicines for diabetes to expand metformin's use in certain patients with reduced kidney function. The current labeling strongly recommends against use of metformin in some patients whose kidneys do not work normally. FDA concluded, from the review of studies published in the medical literature, that metformin can be used safely in patients with mild impairment in kidney function and in some patients with moderate impairment in kidney function.

Recommendations

Major Recommendations

Grades of recommendations (A-D) and levels of evidence (1-4) are defined at the end of the "Major Recommendations" field. Any aspects that the authors of the guideline considered worth highlighting as an area in which conclusive evidence was lacking, or because it addressed particularly relevant clinical aspects are marked as good practice points (GPP).

Cardiovascular Risk Assessment

Calculation of Cardiovascular Risk

B: Use tables adapted and validated for Spain's population.

C: Use the Registre Gironí del Cor (REGICOR) charts to calculate coronary risk in patients who have no coronary disease.

GPP: Do not use REGICOR charts to calculate coronary risk in patients of over age 74, in the presence of known vascular disease, familial hypercholesterolaemia, genetic dyslipidaemia, and in situations in which the total cholesterol level is >320 mg/dl or low-density lipoprotein cholesterol (LDL-c) >240 mg/dl.

GPP: Avoid reference to desirable cholesterol levels and normal lipid ranges in the results of clinical analyses, since their relevance will depend on the patients' particular circumstances, such as previous cardiovascular disease, familial hypercholesterolaemia, combined familial hyperlipidaemia, family histories of early cardiovascular death and, in the absence of these, on the patients' coronary risk.

Definition of Dyslipidaemia

GPP: Further research is needed to help to establish the nature of the association between triglycerides and coronary disease.

Screening for Dyslipidaemia

GPP: Screen the general population for a lipid profile at age 40 in men and age 45 in women to prevent coronary risk.

GPP: Repeat the calculation of coronary risk every four years using the REGICOR chart after age 40 in individuals who are at low risk in the first evaluation.

D: There is no evidence to support the assessment of coronary risk in patients over age 75.

GPP: Assess individual lipid profile in patients with a family history of early vascular disease, familial dyslipidaemia or obesity.

D: An annual lipid profile should be part of the preliminary assessment of patients with high blood pressure or diabetes.

Preliminary Assessment

C: To determine lipid variables such as total cholesterol and high-density lipoprotein cholesterol (HDL-c) is sufficient to estimate coronary risk.

D: Decision-making at the beginning lipid-lowering intervention requires a complete lipid profile obtained after 12-hour fasting.

D: At least two lipid profiles are required before a decision to begin a lipid lowering intervention.

D: Lipid profile determinations should not be made until 12 weeks after acute myocardial infarction and up to 8 weeks after a trauma, surgery, a bacterial or viral infection, and childbirth.

D: Ask patients to remain seated for 5 minutes prior to taking a blood sample. Avoid prolonged venal occlusion. If this is not possible, release the tourniquet one minute after tying it and try the other arm, or wait a few minutes before attempting to extract a sample again.

Ankle-Brachial Index Test

C: When considering drug therapy, the ankle/arm index should be performed on patients with a 10% to 19% coronary risk in the REGICOR chart.

Target Figures for LDL-c

GPP: Target LDL-c levels in primary prevention cannot be based on the existing evidence.

Suspected Cases of Familial Hypercholesterolaemia

GPP: Familial hypercholesterolaemia should be suspected in:

1. Patients with previous cases of familial hypercholesterolaemia in first-degree relatives.
2. In individuals with no previous cases of familial hypercholesterolaemia, with early cardiovascular disease and high cholesterol levels.
3. Individuals >40 with total cholesterol levels above 360 mg/dl or LDL-c levels of >260 mg/dl, and in individuals 30-39 years old with total cholesterol (TC) levels of >340 or LDL >240 mg/dl.

GPP: The recommendation is to determine total cholesterol in all first-degree relatives of patients with familial hypercholesterolaemia, starting at age 10.

GPP: Individuals suspected of familial hypercholesterolaemia should undergo the MedPed test and be referred to specialist care.

Non-pharmacological Measures

Lifestyles

Diet

C-B*: It is recommended to advise the general population and individuals who have suffered a coronary event (*) to follow the Mediterranean dietary model (diet and physical activity). Essentially, this advice should be given in infirmaries.

B: Efforts should be made to promote the daily consumption of fruit and vegetables.

Alcohol

C: It is recommended to advise the general population and patients who have suffered a cardiovascular disease that they should continue to consume alcohol, providing their previous alcohol consumption pattern was low or moderate.

C: The recommended level of alcohol consumption must not exceed 2 units* daily of alcohol in men and 1 unit daily in women.

GPP: Information on the benefits of alcohol must be accompanied by a clear explanation of what one unit of alcohol represents and the adverse effects of heavy drinking.

*1 unit of alcohol is equal to 1 small glass of wine, 1 beer, half a glass of brandy or one coffee with brandy. 2 units of alcohol are equal to 1 glass of wine, a glass of brandy, or one rum and Coke highball or similar.

Physical Activity/Weight Loss

B: The general recommendation is aerobic-intensive exercise such as walking, running, moderately strenuous swimming for at least 30 minutes, five days per week; or strenuous activity for at least 20 minutes, three days per week.

C: In overweight or obese individuals, the recommendation is to reduce calorie intake and to increase physical activity.

Functional Foods

D: To eat fish as a source of omega-3 acids and non-saturated fats as part of the Mediterranean diet.

Medicinal Plants

A: The use of medicinal plants to lower coronary risk is not recommended.

Drug Therapy

Drug Therapy in Primary Prevention

General Population

D: 6 months of dieting and physical activity is recommended prior to beginning the lipid-lowering treatment.

A: Primary preventive measures with low to mild dose statin are recommended in patients of ages 40-75 with >20% coronary risk levels according to the REGICOR equation. Recommendations for a cardio-healthy lifestyle should be given before and/or during pharmacological treatment.

B: Treatment with low to mild statin doses in patients with coronary risks of between 10% and 19%, determined by means of the REGICOR project equation, must be made after treating other cardiovascular risk factors (obesity, high blood pressure, smoking).

B: In patients with coronary risks of between 10% and 19%, determined by means of the REGICOR project equation and the presence of other non-modifiable cardiovascular risk factors (family case histories of premature coronary death, previous cases of family hypercholesterolaemia, preclinical evidence of arteriosclerosis), starting treatment with low to mild statin doses should be considered.

GPP: Therapy should begin with low to mild dose statin in patients with isolated levels of total cholesterol higher than 320 mg/dl and/or LDL-c levels of 240 mg/dl.

GPP B(*) D(**): The recommendation for patients with a prescription for statin therapy in primary prevention and intolerance to statins is to insist on non-drug therapy and to lower the dose or change to another statin. If intolerance persists, the recommendation is to begin fibrate therapy*. Other options may be resins* and/or ezetimibe**.

Women

GPP: In primary prevention, women of ages 40 to 75 at a 10% to 19% coronary risk according to the REGICOR equation should be intervened with preference over other cardiovascular Risk (CVR) factors before they begin lipid-lowering drug therapy.

C: Women of ages 40 to 75 at a risk of coronary disease >20% should begin statin therapy a low to mild doses.

The Elderly

D: Estimating the risk of coronary disease with the information afforded by cholesterol levels is not recommended in patients over age 75.

GPP: In primary prevention, the decision to begin lipid-lowering therapy with statins in patients over age 75 should be made individually and only after assessing the risks, which may be higher than the benefits for which there is no evidence.

GPP: In primary prevention, patients over age 80 previously undergoing treatment with statins, the recommendation is to assess the convenience of interrupting statin therapy on the basis of the patient's life expectancy and quality of life.

Diabetes

C: In diabetic patients with no cardiovascular disease, the coronary risk should be estimated to make decisions on lipid-lowering intervention. When estimating coronary risk in diabetic patients liable for primary prevention, the recommendation is to use the REGICOR project tables for coronary risk (CR).

B: In type 2 diabetic patients age 40 to 75 with a CR of >10% according to the REGICOR project's tables, the recommendation is to begin statin therapy with low to mild doses.

GPP: In diabetic patients over age 75, the recommendation should be made on an individual basis according to the patient's cardiovascular risk factors.

B: The administration of fibrates may be considered in type 2 diabetic patients with a cardiovascular risk of >10% in the REGICOR project table, who do not tolerate statins or for whom statins are contraindicated.

C: In long-term diabetics of >15 years, assess treatment with statins at low to mild dosages, irrespective of coronary risk.

Drug Therapy in Secondary Prevention

Ischaemic Heart Disease

A: In patients with ischaemic heart disease, the recommendation is to begin treatment with mild statin doses, regardless of baseline LDL-c.

B(*) D(**): In patients with ischaemic heart disease and intolerance to statin, the recommendation is to lower the doses or change to a different statin. If the intolerance persists, begin treatment with fibrates*. Other options may be nicotinic acid**, resins**, and/or ezetimibe**.

GPP: After informing the patient of the benefits and risks of treatment, the statin dosage may be increased in patients with ischaemic heart disease in whom LDL-c levels of less than 100 mg/dl have not been attained.

Acute Coronary Syndrome

A: Treatment should begin with mild statin doses in individuals discharged from hospital after acute coronary syndromes, regardless of their total cholesterol and LDL-c base levels.

Cerebrovascular Event

B: In patients with ischaemic ictus of atherothrombotic origin and no ischaemic heart disease, treatment should begin with mild statin doses and recommendations on lifestyle. Begin treatment with statins regardless of baseline LDL-c.

GPP: In patients with a prior ictus in whom LDL-c levels of less than 100 mg/dl have not been attained, the statin dose may be increased after informing the patient of the benefits and risks of treatment.

Peripheral Arterial Disease

B: Mild dose statin is recommended in patients with peripheral arterial disease and related comorbidity.

Therapy for Hypertriglyceridaemia

D: When triglyceride levels fall below 500 mg/dl, clinical decision-making should consider the patient's global risk of cardiovascular disease.

D: The first measures to recommend in patients whose triglyceride levels exceed 200 mg/dl are to lose weight, eat fewer fats, increase physical activity and drink less alcohol or stop altogether.

D: Treatment with fibrates is recommended when triglycerides levels remain higher than 500 mg/dl despite changes in lifestyle.

D: Omega-3 fatty acids may be used as a treatment for hypertriglyceridaemia, in conjunction with fibrates.

Treatment in Patients with Isolated Low HDL-c

A: Aerobic exercise on a regular basis, weight loss if obesity exists, and to quit smoking are recommended to increase HDL-c levels.

GPP: Drug therapy for isolated HDL-c levels is not recommended without taking coronary risk according to the REGICOR chart into account.

Combined Hyperlipidaemia

GPP: The risk of early coronary disease is higher in hereditary forms of mixed hyperlipidaemia. Therefore, a family history of early cardiovascular disease and lipid disorders should be made before beginning treatment. If such cases exist, the patients should be considered as a high cardiovascular risk.

GPP: In primary care, the coronary risk in patients with mixed hyperlipidaemia and no family history should be calculated according to the REGICOR equation. The main purpose of treatment should be to lower coronary risk.

Combined Drug Therapy Indications

GPP: In patients who require a combination of two drugs, statins and low doses of ion-exchange resins may be combined, or ezetimibe can be used in the event of intolerance to the former.

D: Fenofibrates are recommended when a combination of statins and fibrates is required.

GPP: Consider combined treatment in:

- Familial hypercholesterolaemia where adequate control is not secured with a drug.
- Circumstantially, in patients with mixed hyperlipidaemia of family origin.

Adverse Effects of Drug Therapy

Fibrates

D: Discontinuing treatment with fibrates should be considered if a sustained increase in creatinine levels occurs.

D: Gemfibrozil should be the first choice in patients with renal insufficiency who require treatment with fibrates.

Resins

D: Avoid resins in patients with constipation or intestinal disorders.

D: If the patient is taking any other medication concurrently with ion exchange resins, administer the other medication one to four hours after administering the resins.

Initial Assessment and Monitoring of Patients on Drug Therapy

Preliminary Analytical Test Assessment

D: Two lipid profiles are recommended before beginning drug therapy. After drug therapy, one control after an 8-12 week interval is recommended, followed by annual coronary risk assessment in primary care. After adequate control is attained, an annual analysis in secondary prevention is recommended.

D: The glutamic-oxaloacetic transaminase (GOT)/glutamic-pyruvic transaminase (GPT) levels should be determined before beginning treatment with statins or fibrates. If the levels are high, the guideline developers recommend investigating the cause before treatment commences.

B: The creatine phosphokinase (CPK) does not need to be determined before beginning treatment with statins or fibrates in patients with no symptoms.

D: In patients who are starting treatment with statins or fibrates, CPK levels should be determined before beginning treatment in patients who refer unexplainable muscle symptoms and in patients with a high risk of muscle toxicity (patients who are elderly or have a liver disorder, and in the event of potentially myotoxic pharmacological combinations).

D: Starting treatment with statins is not recommended when the CPK level is 5 times higher than the upper limit of normality.

D: GOT, GPT and creatinine levels should be tested, and the presence of cholelithiasis assessed before starting treatment with fibrates.

Regularity of Analytical Tests in Drug Therapy Follow-ups

D: A determination of transaminase 8-12 weeks after commencing treatment with statins is recommended.

D: An annual transaminase determination in patients in treatment with statins is recommended. Statins dosages should be lowered in cases where the transaminase is more than three times higher than normal, and treatment should be discontinued if the high levels persist.

D: Patients should be informed that treatment might be accompanied by muscle symptoms and of the need to request medical advice with their onset.

D: A creatine phosphokinase (CPK) determination should be requested if muscle symptoms appear. Discontinue treatment with statins in cases where CPK is 10 times higher than the upper limit of normality.

D: GOT and GPT values should be determined 8-12 weeks after treatment with fibrates commences and annually thereafter.

D: Routine seric creatinine determinations are not necessary during therapy.

D: Plasma creatinine levels should be determined in patients under treatment with fibrates who take other drugs as well, such as metformin and statins. Therapy should be discontinued if a creatinine increase greater than 1.4 mg/dl in women and 1.5 mg/dl in men is found.

D: Patients should be informed that treatment might be accompanied by muscle symptoms and of the need to request medical advice with their onset. Discontinue treatment with fibrates in cases where CPK is 10 times higher than the upper limit of normality.

Referral Criteria

GPP: Referral to a lipid unit or second-level care is recommended in the event of:

- Suspected cases of familial hypercholesterolaemia
- Severe genetic hyperlipidaemia with abnormally high lipid profiles (total cholesterol [TC]> 400 or LDL-c >260 mg/dl or triglycerides [TG] >1000 mg/dl)
- The need to add a third drug
- The onset of adverse effects that require specialised intervention

Hypercholesterolaemia in Children

Screening

A: Population screening for cholesterol in children and adolescents is not recommended.

GPP: Cholesterol screening is recommended after the age of 10 in children with a first-degree relative with single-gene familiar hypercholesterolaemia.

Non-Drug Therapy: Physical Activity

D: A Mediterranean diet, physical activity and adequate weight control are recommended for children with hypercholesterolaemia and no family record of single-gene dyslipidaemia.

Definitions:

Levels of Evidence

Scottish Intercollegiate Guidelines Network (SIGN) Levels of Evidence for Intervention Studies

1++ High quality meta-analyses, systematic reviews of controlled clinical trials or high quality clinical trials with a very low risk of bias.

1+ Well conducted meta-analyses, systematic reviews of clinical trials or well conducted clinical trials with very low risk of bias.

1- Meta-analyses, systematic reviews of clinical trials or clinical trials with a high risk of bias.

2++ High quality systematic reviews of cohort and case-control studies. Cohort and case-control studies with a very low risk of bias and with a high probability of establishing a causal relationship.

2+ Well-conducted cohort and case-control studies with a low risk of bias and a moderate probability of establishing a causal relationship.

2- Cohort and case-control studies with a high risk of bias and with a significant risk of establishing a non-causal relationship.

3 Non-analytic studies, e.g., case reports and series of cases.

4 Expert opinion.

*Levels of Evidence for Diagnostic Studies**

Ia Systematic review (with uniformity) of Level 1[a] studies

Ib Level 1[b] studies

II Level 2[c] studies; systematic reviews of Level 2 studies

III Level 3[d] studies; systematic reviews of Level 2 studies

IV Consensus, expert reports or opinions and/or clinical experience without explicit critical appraisal; or based on physiology, bench research or "first principles".

[a] Uniformity means that there is very little or no variation in the directions and degrees of results between the individual studies included in the systematic review.

[b] Level 1 studies:

> Studies that compare the test blindly with a certified benchmark (gold standard) and in which a sample of patients reflects the population on whom the test would be applied.

[c] Level 2 studies:

> Studies that deal with a small number of people (the patient sample does not represent the population on whom the test would be applied)
> Studies that use a poor benchmark standard (where "test" is included in the "benchmark", or where the "tests" have an impact on the "benchmark")
> The comparison between the test and the benchmark is not blind
> Case-control studies

[d] Level 3 studies: Studies that present at least two or three of the features included in Level 2

Grades of Recommendation

Scottish Intercollegiate Guidelines Network (SIGN) Grades of Recommendation for Intervention Studies

A At least one meta-analysis, systematic review or clinical trial rated as 1++, directly applicable to the guideline's target population; or a body of evidence consisting of studies rated as 1+ and showing considerable consistency with each other.

B A body of evidence including studies rated as 2++, directly applicable to the guideline's target population, and showing considerable consistency with each other; or evidence extrapolated from studies rated as 1++ or 1+.

C A body of evidence including studies rated as 2+, directly applicable to the guideline's target population, and showing considerable consistency with each other; or evidence extrapolated from studies rated as 2++.

D Evidence level 3 or 4; or evidence extrapolated from studies rated as 2+.

GPP Consensus of the editorial team.

*Grades of Recommendation for Diagnostic Studies**

A Level of evidence Ia or Ib studies

B Level of evidence II studies

C Level of evidence III studies

D Level of evidence IV studies

*Adapted from The Oxford Centre for Evidence-based Medicine Levels of Evidence and the Centre for Reviews and Dissemination Report Number 4 (2001).

Clinical Algorithm(s)

The following algorithms are provided in the appendices of the original guideline document:

- Algorithm for primary prevention care
- Algorithm for secondary prevention
- Algorithm for hypertriglyceridaemia care
- Algorithm for initial appraisal and monitoring of lipid-lowering treatment

Scope

Disease/Condition(s)

- Cardiovascular disease (CVD)
- Dyslipidemia including:
    - Hyperlipidemia
    - Hypertriglyceridemia
    - Hypercholesterolemia

Guideline Category

Evaluation

Management

Prevention

Risk Assessment

Screening

Treatment

Clinical Specialty

Cardiology

Family Practice

Internal Medicine

Pediatrics

Preventive Medicine

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Health Care Providers

Nurses

Physicians

Guideline Objective(s)

To formulate recommendations that will aid decision-making on lipid management as a cardiovascular risk (CVR) factor in the Basque Autonomous Region (CAPV)

Thus, the guideline is intended to:

- Improve health care for CVR patients by suggesting options that are more beneficial to them, based on focusing attention on the best tests and evidence available in scientific literature on lipids as a factor in CVR
- Diminish the differences observed in the treatment and management of lipids as a CVR factor in clinical practice, and to bring the best evidence closer to clinical decision-making

Target Population

Individuals at increased risk for cardiovascular disease (CVD)

Note: This guideline does not address:

The management of individuals with familial hypercholesterolemia and other genetic dyslipidemias
Other cardiovascular risk factors such as smoking, high blood pressure, and diabetes

Interventions and Practices Considered

Diagnosis/Evaluation/Risk Assessment/Screening

1. Cardiovascular risk assessment
2. Use of REGICOR (Registre Gironí del Cor) charts
3. Screening for dyslipidemia
4. Lipid profile determinations
5. Ankle-brachial index trial
6. Screening for cases of familial hypercholesterolemia

Management/Treatment/Prevention

1. Non-drug therapy
    - Lifestyle modification
        - Diet modification

        - Limiting alcohol consumption
        - Physical activity
        - Weight loss
    - Functional foods
    - Omega-3 fatty acids
    - Phytosterols
    - Soy
    - Medicinal plants
2. Drug therapy
    - Statins
    - Fibrates
    - Resins
    - Niacin
    - Ezetimibe
    - Combined therapy
3. Monitoring for treatment response and adverse effects
    - Lipid profiles
    - Transaminase levels
    - Creatine phosphokinase determination

Major Outcomes Considered

- Cardiovascular disease morbidity and mortality
- Survival rate
- Quality of life
- Risk of coronary artery disease
- Blood lipid levels
- Adverse effects of drug therapy

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

2008 Original Guideline

The clinical practice guideline (CPG) is based on a combined strategy. The first step consisted in locating and selecting CPGs drawn up according to acceptably strict standards, by conducting an exhaustive bibliographic search and a subsequent methodological assessment of the selected guidelines using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument.

Ten CPGs were found and assessed, of which four were selected because they met high enough quality criteria to be included and had been published or updated after 2003:

- The Assessment and Management of Cardiovascular Risk. New Zealand Guidelines Group (NZGG).
- Lipid Management in Adults. Institute for Clinical Systems Improvement (ICSI).
- Risk estimation and the prevention of cardiovascular disease. A national clinical guideline. Scottish Intercollegiate Guidelines Network (SIGN).
- The Third report of the National Cholesterol Education Program (NECP) Expert Panel on Detection, Evaluation, and Treatment of High

Blood Cholesterol in Adults (Adult Treatment Panel III). National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services.

Five criteria were used to assess whether the reviews and/or CPGs answered each of the clinical questions adequately and, consequently, to study whether a question raised in the guidelines and/or reviews could be adapted. The criteria were:

- A recommendation's consistency across the guidelines
- The need to update
- The degree of recommendation: recommendation based on solid evidence or expert opinions
- Clarity in the recommendation
- Whether the recommendation could be applied in the guideline developer's context

If it was found that a question had not been answered adequately and, as a result, an *ad hoc* bibliographic search and synthesis of evidence was needed, the method used was the one suggested by the National Institute of Clinical Excellence (NICE) in their guidelines manual:

- Evidence search: Cochrane Library, Medline-PubMed, DARE, Evidence Based Review, EMBASE. The search period was extended until December 2007, depending on the question.
- Evidence assessment by two evaluators, based on the critical reading templates provided by the Scottish Intercollegiate Guidelines Network (SIGN). The features and outcomes of the main studies included are shown in the evidence tables.

2013 Reaffirmation

Medline, Embase, the Cochrane Library, Evidence Updates, UpToDate, Dunamed, Clinical Evidence and the TRIP Database were searched for literature published from 2008 to June 2013.

The developer performed a literature search of primary and secondary sources, clinical practice guidelines (CPGs), clinical trials and systematic reviews. The developer also screened references included in systematic reviews and references of relevant articles were hand-searched for additional studies.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence

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> The comparison between the test and the benchmark is not blind
> Case-control studies

[d] Level 3 studies: Studies that present at least two or three of the features included in Level 2

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Five criteria were used to assess whether the reviews and/or clinical practice guidelines answered each of the clinical questions adequately and, consequently, to study whether a question raised in the guidelines and/or reviews could be adapted. The criteria were:

- A recommendation's consistency across the guidelines
- The need to update
- The degree of recommendation: Recommendation based on solid evidence or expert opinions
- Clarity in the recommendation
- Whether the recommendation could be applied in the guideline developer's context

Evidence from online searches was assessed by two evaluators, based on the critical reading templates provided by the Scottish Intercollegiate Guidelines Network (SIGN). The features and outcomes of the main studies included are shown in the evidence tables in the original guideline document.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

2008 Original Guideline

To prepare the guidelines, a multi-disciplinary working group was formed. Their first task was to select the questions that health professionals usually raise about lipid management in primary and secondary preventive care. The selected questions were sent to a list of 10 external reviewers. Twenty-seven questions referring to adults and 3 questions on the special issue of addressing hypercholesterolaemia in children were selected by consensus (see Table 4 in the original guideline document).

A "formal assessment" or reasoned judgement was used to formulate the recommendations. The working group resolved and wrote the recommendations by consensus.

2013 Reaffirmation

In June 2012, an expert committee was convened to review the currency of the guideline using the following process:

- Formulation of key questions considering the previous version
- Searching for new evidence on the questions through a systematic search of the primary and secondary sources
- Evaluation and synthesis of evidence on the basis of explicit criteria
- External review

Rating Scheme for the Strength of the Recommendations

Grades of Recommendation

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B Level of evidence II studies

C Level of evidence III studies

D Level of evidence IV studies

*Adapted from The Oxford Centre for Evidence-based Medicine Levels of Evidence and the Centre for Reviews and Dissemination Report Number 4 (2001).

Cost Analysis

A formal cost analysis was not performed and published cost-analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Not stated

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is specifically stated for each recommendation (see "Major Recommendations").

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Improvement in the health care of patients with cardiovascular disease by offering treatments based on the best tests and evidence available in the scientific literature
- Reduction in the variability in clinical practice observed in the treatment and management of lipids as a cardiovascular risk factor

Potential Harms

Lipid Screening

The potential benefits of lipid screening should be compared to the adverse effects of lipid-lowering treatments. Labeling individuals as being "at risk" and, therefore, as candidates for drug therapy, may lead to a situation where they are submitted to a series of medical checkups over many years although they will probably never develop the disease. Moreover, the cost-opportunity of carrying out the intervention to the detriment of more beneficial alternatives should be added to the cost of screening and the subsequent intervention.

Adverse Effects of Drug Therapy*

Statins

- Low to mild statin doses have proved to be safe drugs with few secondary effects and of little importance.
- High statin doses are associated with a higher number of adverse effects that cause more patients to abandon therapy, although they are not severe in most cases.
- Statin therapy is not associated with a higher incidence of cancer, although the risk may be increased in patients older than age 75.

Fibrates

- Clofibrate is associated with an increase in non-cardiovascular mortality. It is also related to an increase in the risk of cholelithiasis and cholecystectomy.
- Fibrates are occasionally associated with moderate creatinine elevations.

Resins

- The most frequent adverse effects of resins are gastrointestinal disorders, constipation and pyrosis in particular.
- Resins may interfere in the absorption of certain drugs (thiazide diuretics, furosemide, spironolactone; diltiazem, tricyclic antidepressants, corticoids, digoxin, raloxifene, loperamide and vitamin K).

Niacin

The most frequent adverse effects of niacin are hot flushes, although it also causes gastrointestinal disorders, skin reactions, and muscle symptoms.

*Section 9 in the original guideline document provides detailed data on the adverse effects of drug therapy. Appendix 17 in the original guideline document includes a chart that lists the precautions, counter indications, interactions, and adverse reactions for lipid-lowering drugs.

Contraindications

Contraindications

Contraindications to Statin Therapy

- Hypersensitivity
- Active hepatic disease or persistent and unexplainable elevations of blood transaminase
- Pregnancy
- Breastfeeding period
- Myopathy (for atorvastatin and fluvastatin)

Contraindications to Fibrate Therapy

- Hypersensitivity
- Severe hepatic failure
- Severe renal failure
- Biliary lithiasis
- Known reactions of photosensitivity or phototoxicity while in treatment with fibrates
- Pregnancy
- Breastfeeding period
- Children

Contraindications to Resin Therapy

- Hypersensitivity
- Complete biliary obstruction (noneffective)
- Familial dysbetalipoproteinaemia
- Triglycerides >400 mg/dl

Contraindications to Niacin Therapy

- Arterial haemorrhage
- Active peptic ulcer
- Breastfeeding period

Contraindications to Cholesterol Absorption Blocker Therapy

- Hypersensitivity
- Mild to severe hepatic failure
- Children under age 10
- Breastfeeding period

Contraindication to Omega-3 Fatty Acids Therapy

- Hypersensitivity
- Exogenic hypertriglyceridaemia
- Children
- Pregnancy
- Breastfeeding period

Implementation of the Guideline

Description of Implementation Strategy

The strategy to implement this guideline consists of two stages. To deploy and implement the recommendations in this guideline, the strategy needs to consider the context in which it will be disseminated, as well as the content of the guideline as such.

Another consideration is the availability of tests on the efficacy of the implementation strategies. The literature suggests that the recommendations are more likely to be followed if multiple approach strategies are used.

The clinical practice guideline on lipid management as a cardiovascular risk (CVR) factor will be used by Primary Care professionals and other players who approach the issue in an out-patient context. Therefore, the guideline will need:

- Adequate dissemination in two formats:
  - A condensed version: Distribution of a printed condensed version to all Primary Care professionals and other potential users of the Guideline.
  - A digital condensed version and a full version that can be downloaded from the Osakidetza/Svs intranet and the websites of the Companies that support the guidelines recommendations.
- Presentation of the guideline at health councils in the various health regions.
- Peer-to-peer discussions on the recommendations, led by the guideline's authors.
- Specific workshops on the prescription of statins according to CVR.
- Debates at scientific meetings held by scientific companies.

Implementation Tools

Audit Criteria/Indicators

Chart Documentation/Checklists/Forms

Clinical Algorithm

Foreign Language Translations

Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

San Vicente Blanco R, PÃ©rez Irazusta I, Ibarra Amarica J, Berraondo Zabalegui I, Uribe Oyarbide F, Urraca GarcÃa de Madinabeitia J, Samper Otxotorena R, Aizpurua Imaz I, Almagro Mugica F, AndrÃ©s Novales J, Ugarte Libano R. Clinical practice guideline on the management of lipids as a cardiovascular risk factor. Vitoria-Gasteiz: Basque Health System-Osakidetza; 2008. 215 p.

Adaptation

Four previously published guidelines formed the base of this guideline:

- The Assessment and Management of Cardiovascular Risk. New Zealand Guidelines Group (NZGG).
- Lipid Management in Adults. Institute for Clinical Systems Improvement (ICSI).
- Risk estimation and the prevention of cardiovascular disease. A national clinical guideline. Scottish Intercollegiate Guidelines Network (SIGN).
- The Third report of the National Cholesterol Education Program (NECP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). National Heart, Lung, and Blood Institute National Institutes of Health, U.S. Department of Health and Human Services.

Date Released

2008 Sep (reaffirmed 2013 Jun)

Guideline Developer(s)

Basque Health System - Osakidetza - State/Local Government Agency [Non-U.S.]

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Guideline Committee

Not stated

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Financial Disclosures/Conflicts of Interest

Itziar Pérez, Javier Urraca, Fernando Uribe, Ricardo Samper, Iñaki Berraondo and Ramón Ugarte have stated the absence of a conflict of interest. Ricardo San Vicente has received funds from Pfizer and Novartis to attend conferences; Josu Ibarra received funds from Belmac and Almiral to attend conferences and meetings; Fátima Almagro received funds from MSD and Pfizer to attend conferences and meetings; Javier Andrés received funds from MSD, Pfizer, Schering and Novartis to attend conferences and meetings.

Guideline Status

This is the current release of the guideline.

The Basque Health System-Osakidetza reaffirmed the currency of this guideline in June 2013.

Guideline Availability

Electronic copies: Not available at this time.

Print copies: Available from Osakidetza C/ Alava, nº 45, 01006 Vitoria-Gasteiz, Basque Country (Spain) y Departamento de Sanidad y Consumo, Dirección de Gestión del Conocimiento y Evaluación, Gobierno Vasco, Donostia-San Sebastian, 1 01010 Vitoria-Gasteiz Basque Country (Spain); Email: coordinacion@osakidetza.net, osteba-san@ej-gv.es; Web site: http://www.osakidetza.euskadi.net/v19-oskhome/es .

Availability of Companion Documents

The following forms are available in the appendices of the original guideline document:

- REGICOR charts for calculating coronary risk (in men, women, diabetic men, and diabetic women)
- MEDPED criteria for a medical diagnostic of familial hypercholesterolaemia

In addition, audit indicators are provided in the appendices of the original guideline document.

A Spanish version of the original guideline document is available from the Osakidetza Web site .

Patient Resources

The following forms are available in the appendices of the original guideline document in Spanish and Basque and in the English version:

- Mediterranean diet: recommendations for patients
- Recommendations on losing weight: diet and exercise
- Recommendations for preparing fast yet healthy food

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors

or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This summary was completed by ECRI Institute on November 30, 2010. The information was verified by the guideline developer on January 3, 2011. This summary was updated by ECRI Institute on June 27, 2011 following the U.S. Food and Drug Administration advisory on Zocor (simvastatin). This summary was updated by ECRI Institute on November 22, 2011 following the U.S. Food and Drug Administration (FDA) advisory on Trilipix (fenofibric acid). This summary was updated by ECRI Institute on April 13, 2012 following the U.S. Food and Drug Administration advisories on Statin Drugs and Statins and HIV or Hepatitis C drugs. The currency of the guideline was reaffirmed by the developer in June 2013 and this summary was updated by ECRI Institute on October 23, 2013. This summary was updated by ECRI Institute on April 15, 2016 following the U.S. Food and Drug Administration advisory on Metformin-containing Drugs.

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